Calciphylaxis and the Persistence of Medical Misinformation in the Era of Google

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ABSTRACT

Objectives: We illustrate the important and troubling issue of persistent misinformation and false claims in the medical literature using a frequently cited case inaccurately believed by many to be the first case of calciphylaxis.

Methods: We identified a recurring error in the medical literature in the form of numerous citations of a study from the 1890s of a 6-month-old child with idiopathic infantile arterial calcification that is purported to be the first description of a case of calciphylaxis. We performed searches to determine the frequency of this error. Google Scholar and PubMed were searched for references citing the Bryant and White article. Accuracy of the citations was determined.

Results: A Google Scholar search identified 33 references that incorrectly cite the Bryant and White article as the first description of a case of calciphylaxis. Of the 100 most recent PubMed publications on calciphylaxis, we identified five studies that incorrectly attribute the Bryant and White article as the first description of calciphylaxis, which accounts for approximately 5% of the contemporary literature on this topic.

Conclusions: Medical misinformation such as this is frequently perpetuated. We propose that computational resources could be better used to flag erroneous and contradicted claims to update and correct the literature.

While reviewing the literature on calciphylaxis, one of the authors (S.R.G.) noticed something odd. A large number of studies referred to an article from the late 1890s as the first documented case of the disease.1 What immediately struck us as unusual was the title of the article, which read “A Case of Calcification of the Arteries and Obliterative Endarteritis, Associated With Hydronephrosis, in a Child Aged Six Months.” None of us had ever encountered a case of calciphylaxis in a child, much less a 6-month-old. Neither had any of us ever seen a case in which this possibility was raised in the clinical differential diagnosis. Calciphylaxis is the cutaneous end result of vascular calcification and ischemic necrosis that most commonly occurs in adult patients with chronic renal failure. This phenomenon is more common in diabetics, obese patients, and the malnourished.2 Probing further, it is clear that this child had idiopathic infantile arterial calcification (IIAC), a very rare genetic disorder in which excess calcification occurs, especially in artery walls. Of the approximately 200 cases reported, 85% have died suddenly before 6 months of age. This disease is typically diagnosed postmortem.3 When we discovered, to our surprise, numerous contemporary references citing the Bryant and Hale-White article as the first case of calciphylaxis, we undertook this study to determine the extent of this error and explore its origins. This case illustrates an interesting example of the extent to which medical misinformation can disseminate.

Materials and Methods

We performed Google Scholar and PubMed searches to identify all studies that referenced the Bryant and White
article. We then reviewed the studies for accuracy—specifically whether they referenced the Bryant and White article as an example of calciphylaxis, IIAC, or other disorders. We also performed a PubMed search of recent studies on the subject of calciphylaxis to determine the approximate percentage of contemporary studies that incorrectly (or correctly) reference the Bryant and White article.

Results

A Google Scholar search (performed on August 1, 2013) revealed 127 hits for “calciphylaxis Bryant White.” Google Scholar has been shown in studies to be a more comprehensive search engine than others, with the one disadvantage of also including some extraneous links to personal websites and other websites that do not contain an article. Of the 127 links, 34 were not articles (most were not relevant to the search terms either), six were repeated within the search, 20 were not relevant to the topic of calciphylaxis, 27 were inaccessible, one did not cite the Bryant and White article, and seven were not in English. This left 32 articles in the English literature on the topic of calciphylaxis that cited the Bryant and White article. Twenty-five articles incorrectly reference a Bryant and White 1898 article from the Google Scholar search, five incorrectly reference a Bryant and White 1899 article from the Google Scholar search, three incorrectly reference a Bryant and Hale 1901 article, and one reference an 1898 Bryant and White article that spelled Bryant’s name as “Bryandt.”

One article incorrectly references an 1899 Bryant and White article as describing a case of calciphylaxis; however, in their discussion, they state that “idiopathic arterial calcification of infancy shares features and is included with calciphylaxis in other reviews. However, it differs from calciphylaxis in several respects: the disease may have a genetic basis, the patients are younger, the ischemia is more visceral (most infants die of myocardial infarction), calcium and phosphate levels are normal, and there is no hyperparathyroidism.” The Bryant and White article is not cited in reference to this claim, and it is, therefore, unclear if the authors are aware that this statement contradicts the citation of the Bryant and White article and the above statement.

A PubMed search was performed on “idiopathic infantile arterial calcification” to determine how many studies referenced the Bryant and White article. Of the 53 studies recovered, 25 did not cite the Bryant and White article, and 10 did, with 18 manuscripts unavailable for review.

A PubMed search was performed on “pediatric calciphylaxis” and “child calciphylaxis” to obtain information on the approximate number of reported cases of pediatric calciphylaxis in the literature and the patients’ ages. Eight case reports were identified. The children described were ages 6, 8, 10, 11 (three patients), 12, 16, and 16 years. No cases of calciphylaxis occurring in infants were identified. All children had end-stage renal disease with the exception of one 11-year-old who developed abnormal calcium and phosphate levels as a complication of treatment for acute lymphoblastic lymphoma.

A PubMed search was performed using the search term “calciphylaxis” to identify the most recent 100 studies on the subject of calciphylaxis available for review in English that were evaluated for citation of the Bryant and White article. The studies spanned from 2009 to 2013. Five of these incorrectly cited the Bryant and White article. All five listed it as an 1898 citation.

Discussion

In 1898, Bryant and Hale-White described the clinical course and autopsy findings of a 6-month-old child with “general debility and wasting.” (Curiously, the Bryant and Hale-White reference is most often referred to as Bryant and White, with “Hale” dropped from the hyphenated surname.) The case has characteristic features of IIAC, also known as arterial calcification of infancy, idiopathic arterial calcification of infancy, occlusive infantile arterial calcification, occlusive infantile arteriopathy, and generalized infantile arterial calcification. The disease is extremely rare and has an autosomal recessive pattern of inheritance. Most patients have mutations in the gene ENPP1, which codes for ectonucleotide pyrophosphatase/phosphodiesterase 1, an inhibitor of extracellular calcium deposition. The loss-of-function mutation in ENPP1 leads to unregulated calcification of blood vessels. The prognosis is poor, and many patients die in early childhood with heart failure.

At autopsy, Bryant and White describe large vessels, such as the aorta, showing areas of dilatation and “grittiness” to the touch. The iliac arteries “felt firm, hard and rigid, like pipestems.” “The small vessels of the lower part of the legs and the feet were almost obliterated.” “The brachial artery and its branches, the thyroid, the mesenteric, hepatic and renal arteries were all thickened and rigid.” Microscopic examination of the right anterior tibial artery “showed extensive degenerative changes and calcification, quite the inner five-sixths of it being involved.” A wonderful drawing of the vascular pathology prepared by Thomas G. Stevens is included in the report. These findings are typical of more recently described cases of IIAC.

Interestingly, although Bryant and White’s case continues to be misclassified as a case of calciphylaxis, authors writing on the subject of IIAC correctly cite it as one of the first descriptions of this disease. So, how did Bryant and
White’s case come to be mistaken for a case of calciphylaxis? Part of the answer is clearly due to a change in the definition of calciphylaxis. Today, the term is restricted to the specific necrotizing skin disorder that is seen in some patients with chronic renal failure. This restricted use of the term is very different from the original use of the term.

Selye, in his 1962 monograph entitled *Calciphylaxis*, defines the term as “a condition of induced systemic hypersensitivity in which the tissues respond to appropriate challenging agents with a precipitous, though sometimes evanescent, local calcification.” In his monograph, Selye describes a wide-ranging and what would to most readers be viewed today as largely unrelated group of conditions associated with calcium deposition. Such disparate conditions as myositis ossificans, connective tissue disease, hypervitaminosis D, and calcification of the scrotum are viewed under this broad rubric of calciphylaxis. Clearly, Selye is using the term in a generic sense, as we might use tissue calcium deposition today, rather than to define a specific disease entity.

Although the term calciphylaxis is partly derived from the Greek (*phuláktis*, “a watching, guarding”) meaning “to protect from calcium,” the term had a different connotation and use in the past, as demonstrated by Selye. This is not particular to technical or medical language but to all language in general. We commonly refer to “the meaning” of specific words when, in fact, “meaning” in language is arbitrary and, more important, dynamic. The connection between a word and its meaning is purely a matter of agreement, and the word can be successfully used so long as speakers agree to use it in this particular way.

Semantic change is another feature of language that helps us to understand how language and the use of terms such as calciphylaxis evolve over time. Semantic change is defined as the evolution of word usage, usually to the point in which the modern meaning is radically different from its original use. Many different factors can motivate semantic change, including linguistic, psychological, cultural, and encyclopedic forces. The dynamic nature of language frequently escapes our attention, often because changes in meaning occur slowly and are not appreciated over the span of one’s career or life. For this reason, the term *generational knowledge* has been used to emphasize the seemingly imperceptible change in ideas and knowledge but also applies to language.

We believe these linguistic phenomena help to explain, at least in part, why the term calciphylaxis has a very different meaning today than in 1962, when Selye published his monograph. The possibility of change in meaning of a particular term should be considered when citing or referring to a term currently in usage but extracted from a text or context in the remote past.

We also believe we can trace the origin, or at least the popularization, of the idea that Bryant and White’s case represents the first described case of calciphylaxis to Selye’s monograph. In a section on arteriosclerosis in which he seems to be discussing vitamin D intoxication, Selye mentions, in what appears to be a tangential comment, that “although the syndrome strikingly resembles that of vitamin-D intoxication, it can occur in the absence of any vitamin-D medication.” Selye references the Bryant and White case at the end of this statement, although it is not entirely clear what he is referring to.

Regardless of the precise origin of the idea that Bryant and White described the first case of calciphylaxis, the more important and troubling issue is the presence of persistent misinformation and false claims in the medical literature. What we find so disturbing about this example is the title of the article—in stating the patient is 6 months old—is virtually broadcasting to the reader that this is highly unlikely to be a case of calciphylaxis, as currently used. This suggests the possibility that, at least in some cases, the reference was cited without having been read. If this is the case, it is all the more disturbing since the reference is readily found and available in its entirety with a quick Google search. It turns out that the practice of citing literature that has not been read might be much more common than one might guess. A study using statistical modeling of misprints in scientific citations estimated that only 20% of authors actually read the papers they are citing. The same authors, in another larger study, estimated that 70% to 90% of citations are copied from the reference list from another study. Taking advantage of a misquote that appeared in a textbook, a group of authors determined that the misquote containing errors was copied from the textbook in six (86%) of seven references.

Another prevalent problem in the literature is the persistence of positive references of highly contradicted claims after strong contradictory evidence is presented. One group of authors found studies on vitamin E that cited favorable cardiovascular benefits years after two randomized trials showed no benefit and even potential harm. The same group found 62.5% favorable citations of a study on use of β-carotene for cancer prevention years after evidence contradicted its efficacy. Similarly, the authors found 61.7% of studies with favorable citations regarding an article that proposed a protective effect of estrogen on Alzheimer disease long after this claim was strongly contradicted. Other studies have found persistent citation of fraudulent studies that have been retracted.

The case presented here and other examples of persistence of errors and misinformation in the literature are perplexing in the era of Google. Automated methods to notify authors that a study is no longer correct or controversial are needed. In this era of open access, with more and more clinical and basic research available online to our patients and the general public, it is even more incumbent on the scholarly
community to maintain the integrity of the published literature. We must develop technological approaches to flagging studies containing controversial, erroneous, and highly contradicted claims. Fortunately, as our libraries become electronically centralized, this should be a relatively easy task. Most institutions support electronic libraries rather than personal, divisional, and departmental libraries in print format. (It is, of course, impossible to retract the print version of a study from a personal or departmental collection.)

Computational approaches are being developed to read and interpret information. While some may object to the idea of a computer assisting us in keeping up with our interests and areas of study, when one considers that the PubMed database contains more than 23 million biomedical citations, even the most ardent traditionalist must admit we all need help organizing and digesting the literature.

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